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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,930	05/27/2002	George Pieczenik		7800

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 10/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,930	PIECZENIK, GEORGE	
	Examiner	Art Unit	
	Anne L. Holleran	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *14-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group I (claims 7-13, with linking claims 1-6) in the reply filed on 7/13/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Additionally it is noted that applicant failed to respond to the election of species requirement. On pages 3-4 of the Restriction requirement mailed on 7/5/2005, an election of species requirement was set forth, instructing applicant to elect either an antagonist that is a monoclonal antibody or an antagonist that is a small molecule. **Upon further consideration, the election of species requirement is withdrawn.**

Claims 1-20 are pending.

Claims 14-20, drawn to non-elected inventions, are withdrawn from consideration.

Claims 7-13 with linking claims 1-6 are examined on the merits.

Claim Rejections - 35 USC § 112

2. Claims 2-4 and 8-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite because of the phrase "the hypervariable region". An antibody binding site comprises 6 hypervariable regions (CDRs). Thus, "the hypervariable region" lacks antecedent basis.

Claim 3 is indefinite because of the phrase "wherein the monoclonal antibody is chimerized and humanized". Usually, chimerization refers to a process of producing an antibody with a non-human variable region and a human constant region, whereas humanization refers to processes such as CDR grafting, where most of the antibody contains human sequences. Does applicant intend "chimerized ***or*** humanized"?

Claims 2, 3 and 4 are indefinite because it is not clear what the binding specificity of the monoclonal antibody (claims 2 and 3) or of the small molecule is. The claim 2 recites "monoclonal antibody specific for EGFRML", which would indicate that the antibody is one that binds to an EGFR ligand. Claim 4 recites "a small molecule that binds specifically with EGFRML". In contrast the specification appears to be teaching that the contemplated antibodies and small molecules are molecules that bind to the EGFR (and also interfere with the function of the EGFR to bind ligand). For example at page 9, paragraph 45, the specification states "Antibodies may be made from the desired receptor as an immunogen...". The antibodies of Masui and of Baselga (cited in paragraph 59 on page 11) are antibodies that bind to the EGFR, not to EGFR ligands. Also, in the specification at pages 11-12 of the specification, paragraph 60, the specification asserts that anti-EGFR-ligand antibodies can be synthesized from the nucleotide sequence by the method provided in Wells et al in Int. J. Cancer 60, 137-144, 1995. PCT application WO 96/40201 is also referred to. However, both of these documents teach antibodies that bind to the EGFR, not to EGFR ligands.

Claims 4 and 12 are indefinite because the term "small molecule" is not defined in the specification. The specification teaches that "small molecule" may have any molecular weight. Therefore, it is not clear why these compounds are referred to as "small molecules".

Claim 8 is indefinite because it depends from itself. For purposes of comparison with the prior art, claim 8 is interpreted to depend from claim 7.

Claim 8 is also indefinite because of the phrase "with null options included". The specification fails to define what "null options" are. Therefore, the steps of the methods encompassed by claim 8 are not clearly set forth.

3. Claims 1, 4-10, 12 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods comprising administering an anti-EGFR antibody in combination with radiation, does not reasonably provide enablement for methods comprising administering any compound that might fall within the scope of the term "small molecule" in combination with radiation, where the purpose of the method is the inhibition of the growth of refractory tumors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is that the specification provides inadequate guidance to enable the full scope of methods for treating human patients with refractory tumors where the methods comprise using the multitude of molecules that are encompassed by the term "small molecule".

The specification teaches that antagonists useful in the present invention be small molecules, and that some examples of small molecules include organic compounds, organometallic compounds, salts of organic and organometallic compounds, saccharides, amino acids, and nucleotides. Additionally, the specification teaches that further to the definition provided, small molecules shall include molecules with a molecular weight that is not greater

than 600, but it is emphasized that small molecules can have any molecular weight. Preferably, the small molecules inhibit the growth of refractory tumor cells that express EGFR/HER1. Thus, definition provided for the term "small molecule" does not provide guidance on the range of molecular weight (because small molecules can have any molecular weight); and does not define the biological activity (because "preferably" the small molecules inhibit the growth of refractory tumors) of the compounds encompassed by the term "small molecule". The structural properties of the compounds encompassed by the term "small molecule" are not well defined because the specification teaches that small molecules may be "lipids, oligosaccharides, oligopeptides, and oligonucleotides, and their derivatives having a molecular weight of 600 or less". Thus, the structure of the small molecules is described only in terms of broad classes of molecules.

The prior art teaches a peptide that may be used to antagonize EGFR ligand activity (see Greene, below), which peptide is a peptide derived from a CDR from an antibody that binds Her2. Also, in the prior art are quinazolines (see Arnold below). However, encompassed by the claims are methods using small peptides that might be derived from EGF or TGFα, ligands of EGFR. Groenen (Groenen, L.C. et al., Growth Factors, 11: 235-257, 1994) teaches that it seems unlikely that agonists or antagonists based on short fragments of EGF or TGF-α can be developed (see page 252, 2nd column). Nakamura teaches that one reason for a lack of success in using fragments of EGF or TGF-α is that the fragments are too short to form the tertiary structure required for binding to the EGFR (see Nakamura, T. et al. Journal of Biotechnology, 116: 211-219, 2005; page 212 1st column). Thus, while the prior art teaches some examples of compounds that would be encompassed by the term "small molecule", the prior art also teaches that further experimentation is required, especially in the development of peptide-based EGFR antagonists.

Also, these examples provided provide no guidance to one of skill in the art with respect to antagonists that are lipids, oligosaccharides or oligonucleotides. Therefore, the further experimentation that would be required to enable the full scope of the claimed methods with respect to claims that read on the use of small molecules that are peptides, lipids, oligosaccharides or oligonucleotides would be undue experimentation because the claims encompass the use of broad classes of molecules for which not one example of an antagonist has been provided and because in the field of peptide-based EGFR antagonists, further experimentation is required to discover useful EGFR antagonists.

Claim Rejections - 35 USC § 102

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1, 5- 9, 11 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Bonner (Bonner, J.A. et al., Proceedings of the ASCO (2000) 19: 4a, abstract 5F) as evidenced by Herbst (Herbst, R.S. et al, Expert Opin. Biol. Ther. (2001) 1(4): 719-732).

Bonner teaches a method of treating head and neck cancer patients with a combination of radiation therapy and an anti-EGFR monoclonal antibody, IMC-C225. Head and neck cancers are known to be refractory to treatment as evidenced by the teachings of Herbst (see page 719, "fewer than 30% of [...] patients will be cured"). Therefore, Bonner teaches the method as claimed.

Please note that this rejection was not applied to claims 2 and 3, because claim 2 recites that the monoclonal antibody is "specific for EGFRML". This was interpreted as reading on a

method using an antibody that binds to an EGFR ligand. IMC-C225 binds to the EGF receptor. If applicant amends claims 2 and 3 so that they read on methods using an antibody that bind to the receptor, this rejection will be applied to claims 2 and 3.

5. Claims 1, 5-10, 12, and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Greene (U.S. 6,417,168; issued Jul. 9, 2002; effective filing date Mar. 4, 1998) as evidenced by Stern (Stern, J.I. et al. Expert Rev. Anticancer Ther. 6(5): 755-767, 2006).

The claims are broadly drawn to methods of inhibiting the growth of refractory tumors that are stimulated by a ligand of epidermal growth factor receptor, comprising treating human patients with an effective amount of an EGFR/Her1 mitogenic ligand antagonist in combination with radiation. The specification teaches that an EGFRML antagonist is any substance that inhibits the stimulation of EGFR/HER1 by a mitogenic ligand (page 6, paragraph 33).

Greene teaches and claims a method of treating a p185-mediated tumor comprising administering, in combination with radiation, a peptide that inhibits the formation of erbB protein dimers, where the dimers may p185/EGFR heterodimers (see claims 1 and 14). One of the activities of EGFR is to form heterodimers with p185(Her-2) in response to ligand stimulation. Greene teaches that radiation therapy protocols and parameters known in the art may be used (see column 18, lines 30-52). Greene teaches that tumors that may be treated are glial brain tumors and prostate cancers (see column 20, lines 4-18). Gliomas are known in the art to be refractory to treatment (see Stern, abstract). Greene teaches treatment of radioresistant tumors, which is encompassed by claim 5, that is drawn to the treatment of a refractory tumor that has been treated with radiation (see column 48, line 21 – column 49, 34). Thus, Greene

teaches a method comprising the administration of an EGFRML antagonist in combination with radiation.

6. Claims 1, 7, 8 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Arnold (U.S. 5,736,534; issued April 7, 1998) as evidenced by Herbst (Herbst, R.S. et al, Expert Opin. Biol. Ther. (2001) 1(4): 719-732).

Claims 1, 7, 8 and 12 are broadly drawn to methods of inhibiting the growth of refractory tumors, comprising treating human patients with an effective amount of an EGFR/HER1 mitogenic ligand antagonist in combination with radiation. Arnold teaches methods of treatment of cancers such as renal, liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, lung, vulval, thyroid, hepatic carcinomas, sarcomas, glioblastomas, and various head and neck tumors (see col. 20, lines 24) comprising administering quinazolines of Formula I (see col. 2, lines 15-20) in combination with radiation (see column 20, lines 31-37). Arnold does not explicitly mention "refractory tumors". However, as evidenced by Herbst (see page 719, "fewer than 30% of [...] patients will be cured"), tumors such as head and neck tumors are often refractory to treatment. Thus, Arnold teaches methods that are the same as that claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 1, 5-11, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang (Huang, S.-M. et al., Clinical Cancer Research, 6: 2166-2174, 2000) in view of Herbst (Herbst, R.S. et al, Expert Opin. Biol. Ther. (2001) 1(4): 719-732).

The claims encompass or are drawn to methods for inhibition of growth of refractory tumors that are stimulated by a ligand of EGFR, comprising treating a human patient with a combination of radiation and an EGFR antagonist that may be a monoclonal antibody.

Huang teaches a method of treating mice implanted with human squamous cell carcinoma of the head and neck with a combination of radiation therapy and C225, a chimeric monoclonal antibody that binds to the EGFR. The human squamous cell carcinoma cell lines were established from biopsies of head and neck cancer patients. Herbst teaches that cancers of the head and neck are refractory to many forms of cancer treatment (see above). Huang fails to teach treatment of human patients.

However, because Huang teaches his method using cell lines derived from biopsies of head and neck cancer patients, and because Huang teaches that the combination of radiation and anti-EGFR antibody therapy was successful in suppressing the growth of the SCC xenografts, it

would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used Huang's method to treat human patients with head and neck cancer, which is a refractory cancer.

Claims 8-10 include limitations concerning the order in which the antibodies and radiation are administered and the source of the radiation. The combination of Huang and Herbst does not teach every combination of therapy as recited in claims 8-10. However, it would have been obvious to one of ordinary skill in the art of treating cancer patients how to optimize a treatment schedule. Such optimization of treatment does not appear to add an inventive step to the claimed inventions. See MPEP 2144.05: A. Optimization Within Prior Art Conditions or Through Routine Experimentation

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum

combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Please note that this rejection was not applied to claims 2 and 3, because claim 2 recites that the monoclonal antibody is "specific for EGFRML". This was interpreted as reading on a method using an antibody that binds to an EGFR ligand. C225 binds to the EGF receptor. If applicant amends claims 2 and 3 so that they read on methods using an antibody that bind to the receptor, this rejection will be applied to claims 2 and 3.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry

Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600..

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
September 17, 2006

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